PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	KAMINSKI, Joseph M.
Application No.	:	10/521,936
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For	:	TRANSPOSON-BASED VECTORS AND METHODS OF NUCLEIC ACID INTEGRATION
Examiner	:	Kevin Kai Hill
Art Unit	:	1633
Confirmation No.	:	6143
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Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
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APPELLANT'S BRIEF (37 C.F.R. § 41.37)

Sir:

Appellants appeal from the final rejection of Claims 1, 5, 6, 15, 18, 20 and 23 of the above-identified application. This Brief on Appeal is filed in support of Appellant's appeal from the Final Office Action mailed July 6, 2009, rejecting the claims. The appeal is proper because the claims have been rejected at least twice. Consideration of the application and reversal of the rejections are respectfully urged. Submitted with this brief is authorization to pay the fee for filing a brief in support of an appeal as set forth in 37 C.F.R. § 41.20(b)(2) and extension fees set forth in 37 C.F.R. § 1.17(a).

TABLE OF CONTENTS

I. STATEMENT OF THE REAL PARTY IN INTEREST

The real party in interest in the above-identified application is the Appellant's assignee, Manoa Biosciences Inc., a Delaware corporation with its principal place of business at: 1717 Mott-Smith Drive #3213, Honolulu, Hawaii 96822.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals known to Appellant's attorney and the assignee of the instant application, that directly affect, that would be directly affected by, or that may have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 1-6, 15, 18-20 and 23-26 are pending. Claims 2-4, 19 and 24-26 have been withdrawn. Claims 7-14, 16-17 and 21-22 are cancelled.

Claims 1, 5, 6, 15, 18 and 20 stand rejected as allegedly being unpatentable under 35 U.S.C. § 103 over Handler *et al.* (1998. *PNAS* 95:7520-7525, "Handler") in view of Kim *et al.* (U.S. Patent No. 6,479,616, "Kim"), Katz *et al.* (1996. *Virology* 217:178-190, "Katz"), Elledge *et al.* (U.S. Patent No. 6,828,093, "Elledge") and Grigliatti *et al.* (U.S. Patent Publication No. 2002-0116723, "Grigliatti").

Claim 23 stands rejected as allegedly being unpatentable under U.S.C. §103(a) over Handler in view of Kim, Katz, Elledge and Grigliatti as applied to Claims 1, 5-6, 15, 18 and 20 and further in view of McFarlane (1996. *Transgenic Res* 5(3):171-177, "McFarlane").

Claims 1, 5, 6, 15, 18, 20 and 23 are presently appealed under 35 U.S.C. § 134.

IV. STATUS OF AMENDMENTS

No after-final amendments have been submitted by Appellants. The claims shown in the accompanying Appendix are an accurate representation of the pending claims.

V. SUMMARY OF CLAIMED SUBJECT MATTER

This summary is presented in compliance with the requirements of 37 C.F.R. § 41.37(c)(1)(v), mandating a "concise explanation of the subject matter defined in each of the independent claims involved in the appeal." Nothing stated within this summary is to be

interpreted as changing the specific language of the claims, nor is the language of this summary intended to be considered so as to limit the scope of the claims in any way.

Independent Claim 1 is drawn to a novel composition containing a nucleic acid construct that includes a transgene flanked by two terminal repeat sequences, wherein the terminal repeat sequences are derived from piggyBac transposon, and a nucleic acid sequence encoding a chimeric integrating enzyme under the control of a promoter element in which the chimeric integrating enzyme comprises a DNA binding domain and an enzymatic integrating domain, wherein the DNA binding domain is derived from a zinc finger domain and wherein the enzymatic integrating domain is derived from piggyBac transposase. The composition allows site-specific integration of a transgene into a host genome by coupling the binding specificity of a zinc finger domain with the catalytic capabilities of piggyBac transposase, and it accomplishes this in an efficient manner using a single plasmid construct. In contrast, the currently existing systems employ two plasmids (a "helper" vector encoding a transposase and a "donor" plasmid containing the transposon) that are not as effective in integrating the transposon. Furthermore, the development of the single plasmid system was a technically challenging feat that was accomplished after much effort and experimentation.

Support for Claim 1 is found throughout the specification, for example, at page 9, lines 21-33 (paragraph 52); page 11, lines 13-16 (paragraph 59); page 14, lines 1-22 (paragraphs 72-74); page 16, lines 5-13 (within paragraph 82); page 29, lines 15-16 (paragraph 121); and Example 18 of the specification as filed as well as in the claims as originally filed.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1, 5, 6, 15, 18 and 20 were rejected as allegedly being unpatentable under 35 U.S.C. § 103 over Handler *et al.* (1998. *PNAS* 95:7520-7525, "Handler") in view of Kim *et al.* (U.S. Patent No. 6,479,616, "Kim"), Katz *et al.* (1996. *Virology* 217:178-190, "Katz"), Elledge *et al.* (U.S. Patent No. 6,828,093, "Elledge") and Grigliatti *et al.* (U.S. Patent Publication No. 2002-0116723, "Grigliatti").

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VII. ARGUMENT

The Examiner maintained the rejection of Claims 1, 5-6, 15, 18 and 20 under 35 U.S.C. §103(a) as allegedly unpatentable over Handler *et al.* (1998. *PNAS* 95:7520-7525, hereinafter referred to as "Handler") in view of Kim *et al.* (U.S. Patent No. 6,479,616, hereinafter referred to as "Kim"), Katz *et al.* (1996. *Virology* 217:178-190, hereinafter referred to as "Katz"), Elledge *et al.* (U.S. Patent No. 6,828,093, hereinafter referred to as "Elledge") and Grigliatti *et al.* (U.S. Patent Publication No. 2002-0116723, hereinafter referred to as "Grigliatti"). The rejection of Claim 23 under U.S.C. §103(a) was also maintained as allegedly being unpatentable over Handler in view of Kim, Katz, Elledge and Grigliatti as applied to Claims 1, 5-6, 15, 18 and 20 and further in view of McFarlane (1996. *Transgenic Res* 5(3):171-177, hereinafter referred to as "McFarlane").

Standard for Obviousness

The Patent and Trademark Office has the burden under section 103 to establish a *prima facie* case of obviousness.[1] To establish a *prima facie* case of obviousness, the Examiner must clearly articulate the reason(s) why the claimed invention would have been obvious.[2] The obviousness analysis should be made explicit: "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."[3] The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. As such, "[i]f a person of ordinary skill can implement a ***predictable*** variation, §103 likely bars its patentability."[4]

Furthermore, "[o]bviousness cannot be predicated on what is unknown."[5] It is impermissible hindsight to use the present application as a template to piece together prior art

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[1] See, e.g., In re Piasecki, 745 F.2d 1468, 1471-1472, (Fed. Cir. 1984).
[2] See KSR International Co. v. Teleflex, Inc., 550 U.S. 398 (2007), and M.P.E.P. § 2142.
[3] Id. at 418, quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006).
[4] Id. at 412 (emphasis added), and M.P.E.P. § 2143.01 (III).
[5] In re Spormann, 363 F.2d 444, 448 (CCPA 1966).

teachings to allege obviousness.[6] Articulated reasoning with some rational underpinning safeguards against using hindsight in an obviousness analysis.[7]

Thus, for a *prima facie* case of obviousness to be proper, the person of ordinary skill in the art must be motivated to make the claimed combination, and have a reasonable expectation of success, without the benefit of prior knowledge of the contents of the disclosure or the claims.

(1) The Examiner's application of prior art that he previously determined to be a nonobvious variant of the elected species is legal error

The Examiner has maintained his reliance on a cited reference directed to integrases (Katz) to illustrate the alleged obviousness of claims directed to transposases. In order to accomplish this, the Examiner relies on Elledge, Coates *et al.* (2005. *Trends in Biotechnology* 23(8):407-419, hereinafter referred to as "Coates") and the instant specification. In so doing, the Examiner has reversed his own previous determination that transposases, recombinases and integrases are ***not*** obvious variants of each other.

At the outset of prosecution in this case, the Examiner required a species election between transposases, integrases and recombinases "due to their mutually exclusive characteristics," holding that "the species are not obvious variant of each another based on the current record" and that "the prior art applicable to one species would not likely be applicable to another species."[8] For example, the Examiner states:

> *Prior to the invention, the art had long-recognized that each integrating enzyme possesses its own special technical feature because each enzyme recognizes a distinctly different nucleic acid sequence, thereby generating site-specificity for integration and/or excision of the nucleic acid.*[9]

Appellant understood this to be a final determination, and fully complied with the species election in good faith, neither traversing nor petitioning the requirement. Appellant reasonably understood that the Examiner had determined these to be "patentably distinct species" and would therefore not raise prior art directed to integrases and recombinases against claims directed to transposases. During substantive prosecution, however, the Examiner nonetheless reversed his

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[6] See In re Fritch, 972 F.2d 1260, 1266 (Fed. Cir. 1992).

[7] See In re Kahn, 441 F.3d 977 (Fed. Cir. 2006) and M.P.E.P. §2143.01(I).

[8] *See* Office Action mailed December 12, 2007 ("Election Requirement") at pages 2-3; Appellant's' Response filed April 20, 2009, pages 5-7.

[9] *See* Election Requirement at page 2-3.

determination in order to expand the universe of prior art available to establish obviousness. It was error to do so.

Appellant has failed to find any previous case in which the Board sustained an obviousness rejection that was based on art disclosing a nonelected species, following an *explicit* determination by the Examiner that the cited species and the elected species were non-obvious variants.[10] This is unsurprising: general principles of estoppel should apply, and the Examiner should not be able to reverse an express legal holding on which Appellant has detrimentally relied, merely in order to facilitate a strained obviousness rejection.

The Examiner attempts to justify his legal gymnastics on the grounds that his previous determination was "prior to search and examination of the claims."[11] This is immaterial. Appellant recognizes that the PTO must have some means for controlling its administrative matters, and that election of species requirements are one mechanism for doing this. But, as the Examiner himself noted, Appellant's compliance with the requirement relieved him of an "examination and search burden."[12] The Examiner has materially benefitted from Appellant's compliance with the requirement, and the Examiner should not now be allowed to change his mind, and thereby avoid the consequences of his own determination. Appellant is bound by it; the Examiner should be as well.

(2) The facts adduced are insufficient to support a prima facie case of obviousness

In the outstanding Final Office Action, the Examiner asserts that "at the time of the invention, piggyBac transposase was an art-recognized species within the genus of **site-specific recombination enzymes** comprising transposases, integrases and recombinases."[13] This is distinct from the assertion that the Examiner made in the Final Office Action dated December 18, 2008, in which the Examiner stated that "[n]either Handler et al, Kim et al nor Katz et al teach that the genus of integrases and recombinases embraces transposases" and relied on the disclosure of Elledge, a U.S. patent, to teach that **site-specific recombinases** include

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[10] In *Ex parte Capps*, No. 2008-001800 (May 29, 2009), for example, the obviousness rejection was based on a reference disclosing the elected species, and thus the Board's statement relating to effect of a species requirement on applicable prior art is merely dicta with respect to the issue presented in this appeal.

[11] *See* Final Office Action, page 5.

[12] *See* Election Requirement, page 3.

[13] Final Office Action, page 5, lines 22-24.

recombinases, transposases and integrases. This distinction is important: the Examiner relied on the disclosure of Elledge, which defines **site-specific recombinases** (not site-specific recombination enzymes generally) to assert that art directed to recombinases and integrases could be used in an obviousness rejection for claims directed to piggyBac transposase. Thus, the reliance on Elledge for obviousness no longer appears proper in view of the Examiner's current arguments.

In addition, as discussed in Appellant's response filed April 20, 2009, Elledge incorrectly defines the term "site-specific recombinase."[14] At best, Elledge was acting as his own lexicographer in defining this term for the purposes of describing the claimed invention. However, this is not a reflection of what the Examiner himself correctly described as generally understood in the art, namely, that these enzymes are not interchangeable or obvious variants of each other.

Finally, Elledge published as U.S. Patent No. 6,828,093 on December 7, 2004, which post-dates the priority date of the instant application (July 24, 2002). Accordingly, the Examiner has improperly applied Elledge as a critical reference to reject the claims under 35 U.S.C. §103.

Coates states that "[v]iral integrases, transposases and site-specific recombinases mediate the integration of virus genomes, transposons or bacteriophages into host genomes."[15] Coates then goes on to describe each system ("Viral DNA integration systems," "Transposon-based DNA integration systems," "Recombinase-based DNA integration systems") under separate headings. Thus, contrary to Elledge's definition and the Examiner's assertion, it is clear from Coates that "site-specific recombinases" are distinct from viral integrases and transposases and do not encompass them. In addition, when read in its entirety, it is clear from Coates that a person of ordinary skill in the art would consider transposases, recombinases and integrases to be distinctly different in both evolutionary and mechanistic terms. The Examiner asserts that the same functional result is achieved, namely site-specific integration. However, the Examiner fails to take into account what he had previously recognized, namely, that "each integrating enzyme possesses its own special technical feature because each enzyme recognizes a distinctly different

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[14] *See* Elledge, Col. 17, lines 16-19 ("The term 'site-specific recombinase' refers to enzymes that recognize short DNA sequences that become the crossover regions during the recombination event and includes recombinases, transposases and integrases.")

[15] *See* Coates, page 407, second column, first full paragraph.

nucleic acid sequence, thereby generating site-specificity for integration and/or excision of the nucleic acid."[16] Accordingly, the different mechanisms and specificity of integration among transposases, recombinases and integrases would not make it obvious to the skilled artisan to substitute one type of enzyme for another, or to apply the teachings of one type of enzyme to either of the other types.

Appellant's own application simply teaches that "[i]ntegrating enzymes can be any enzyme with integrating capabilities." (*See* page 9, paragraph 51). This disclosure does not, as the Examiner appears to believe, support the view that transposases and integrases are obvious variants of one another.

Accordingly, even on the factual record provided by the Examiner, no legal conclusion of obviousness is justified.

(3) Even if the Examiner has established a prima facie case, Appellant has rebutted it

Appellant's description of each of Handler, Kim, Katz, Elledge and Grigliatti as described in Appellant's response filed April 20, 2009, was intended to illustrate the impropriety of combining these references and the fact that the combination does not teach or suggest the claimed subject matter. The claims relate to a composition containing a single nucleic acid construct that includes (i) a transgene, flanked by piggyBac transposon-derived terminal repeats, to be integrated into a target host genome for non-transient expression in the host, and (ii) a nucleic acid sequence that encodes a chimeric integrating enzyme that catalyzes integration of the transgene into the target host genome. The chimeric integrating enzyme, which refers to a genetically engineered recombinant protein wherein the domains thereof are derived from heterologous coding regions, includes a zinc-finger-derived DNA binding domain as well as an enzymatic integrating domain derived from piggyBac transposase.

Handler is directed to a two-vector system, wherein a first vector encodes a transgene (the medfly *w* gene) and a second vector encoding the normally regulated piggyBac transposase. Kim is primarily directed to chimeric zinc-finger proteins, which may include a regulatory domain, such as, for example an integrase or recombinase. Katz teaches a construct in which the DNA-binding domain of LexA repressor protein is fused to the catalytic domain of avian

[16] Election Requirement, pages 2-3.

sarcoma virus (ASV) integrase enzyme. Elledge defines the term "site-specific recombinase" to refer to enzymes that include recombinases, transposases and integrases. Grigliatti references piggyBac transposase in regard to the creation of inducible transposase producing cell lines, which is performed by creating transposase constructs in which a transposase gene is inserted downstream of a promoter and transformed into cell lines. As discussed above, Appellant believes that the art directed to integrases and recombinases (Kim, Katz) is not applicable to piggyBac transposase in view of the species election. Elledge has already been addressed in terms of its incorrect definition of "site-specific recombinase." The remaining combination of references, Handler and Grigliatti, do not teach or suggest the claimed subject matter of a single nucleic acid construct containing a transgene flanked by piggyBac transposon-derived terminal repeats and a region that encodes a chimeric integrating having a zinc-finger-derived DNA binding domain and an enzymatic integrating domain derived from piggyBac transposase. Accordingly, Appellant asserts that the claims are not obvious over the relevant combination of references.

In view of the foregoing, Appellant submits that the cited references, either alone or in combination, do not teach or suggest all the features of the claims and therefore a *prima facie* case of obviousness has not been established. Appellant respectfully submits that Claims 1, 5-6, 15, 18, 20 and 23 are patentable over the cited combination of references. Withdrawal of the rejection of claims under 35 U.S.C. §103(a) is respectfully requested.

VIII. CONCLUSION

For the reasons provided herein, Appellant submits the Examiner has improperly rejected the claims that are the subject of the present appeal under 35 U.S.C. § 103. Accordingly, withdrawal of the rejections by the Examiner or reversal of the Examiner's rejection of the claims under appeal by the Board is respectfully requested.

Appellant believe a generic claim to be allowable. Accordingly, Appellants further respectfully request consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 C.F.R. §1.141.

The Commissioner is hereby authorized to charge the fee for filing a brief in support of an appeal as set forth in 37 C.F.R. § 41.20(b)(2), extension fees set forth in 37 C.F.R. § 1.17(a), and any other fees, or credit any overpayments to Deposit Account No. 04-0258.

Respectfully submitted,

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Date: September 3, 2010

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IX. APPENDIX OF CLAIMS INVOLVED IN THE APPEAL

1. **(Previously presented)** A composition comprising a nucleic acid construct comprising:

a transgene flanked by two terminal repeat sequences, wherein the terminal repeat sequences are derived from piggyBac transposon; and

a nucleic acid sequence encoding a chimeric integrating enzyme under the control of a promoter element, the chimeric integrating enzyme comprising a DNA binding domain and an enzymatic integrating domain, wherein the DNA binding domain is derived from a zinc finger domain and wherein the enzymatic integrating domain is derived from piggyBac transposase.

2. **(Withdrawn)** The composition of claim 1, wherein the promoter element is a promoter/enhancer.

3. **(Withdrawn)** The composition of claim 1, wherein the promoter is a site-specific promoter.

4. **(Withdrawn)** The composition of claim 3, wherein the site-specific promoter can be selected from at least the group consisting of the glial fibrillary acetic protein (GFAP) promoter, myolin basic (MBP) promoter, MCK promoter, NSE promoter, nestin promoter, synapsin promoter, Insulin 2 (Ins2) promoter, PSA promoter, albumin promoter, TRP-1 promoter, the tyrosinase promoter, the EIIA promoter, a promoter specific for breast tissue, such as the WAP promoter, a promoter specific for ovarian tissue, such as the ACTB promoter, or a promoter specific for bone tissue.

5. **(Original)** The composition of claim 1, wherein the promoter is inducible.

6. **(Previously presented)** The composition of claim 5, wherein the inducible promoter can be selected from at least the group consisting of human heat shock promoter, Egr-1 promoter, tetracycline-responsive promoter, cre-lox recombinase system, and the human glandular kallikrein 2 (hK2) promoter.

7. **(Cancelled)**

8. **(Cancelled)**

9. **(Cancelled)**

10. **(Cancelled)**

11. **(Cancelled)**

12. **(Cancelled)**

13. **(Cancelled)**

14. **(Cancelled)**

15. **(Previously presented)** The composition of claim 1, wherein the DNA-binding domain is a host-specific DNA binding domain.

16. **(Cancelled)**

17. **(Cancelled)**

18. **(Previously presented)** The composition of claim 15, wherein the host-specific DNA binding domain is fused to the N-terminus of the enzymatic integrating domain.

19. **(Withdrawn)** The composition of claim 15, wherein the host-specific binding domain is fused to the C-terminus of the enzymatic integrating domain.

20. **(Previously presented)** The composition of claim 1, wherein the nucleic acid sequence encoding the chimeric integrating enzyme is located outside the terminal repeats.

21. **(Cancelled)**

22. **(Cancelled)**

23. **(Original)** The composition of claim 1, further comprising a homologous sequence that is homologous to the host DNA.

24. **(Withdrawn)** The composition of claim 23, wherein the homologous sequence is located outside the terminal repeats.

25. **(Withdrawn)** The composition of claim 1, further comprising a protein binding sequence and a separate nucleic acid encoding two DNA binding domains.

26. **(Withdrawn)** The composition of claim 1, further comprising a protein binding sequence and a separate nucleic acid encoding a DNA binding domain and a protein-binding domain.

X. EVIDENCE APPENDIX

None.

XI. RELATED PROCEEDINGS APPENDIX

None.